A new era with advanced immunotherapy

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With the poor prognosis and high recurrence rate of pancreatic cancer, the need for new effective treatments remains at the forefront of the attention of many researchers worldwide. As of today, this continues to be one of the most lethal cancers, the main hope for patients being surgery and consequent chemotherapy, an option that is only available for 15–20% of patients due to the late diagnosis of the majority of those affected. Even after surgical resection, the treatment approach has room for improvement, especially considering the high recurrence rates and relatively modest 5-year survival rates of 43.2% observed after adjuvant-modified FOLFIRINOX in highly selected patients (1,2).

In the last decade, tumor-specific and personalized treatments have experienced rapid growth; clear examples are the already successfully marketed chimeric antigen receptor (CAR) T cell therapy, initially designed for lymphomas and leukemias, that is slowly but steadily also gaining ground in solid tumors, as well as a wide range of immunotherapy varieties (3). However, this approach of training the patient's immune system to recognize and eliminate cancer cells requires further effort. Pre-clinical studies show more optimistic results than translational studies, indicating the complexity of bridging laboratory findings into clinical practice. The suppressive microenvironment, the absence of specific immune cells, drug-induced tolerance, and the risk of developing cytokine release syndrome (CRS) continue to challenge the effectiveness and broader application of immunotherapy. Particularly in patients with minimal residual disease (MRD), where the tumor burden is minimal following primary treatment, immunotherapy holds substantial promise. It could exert more pronounced effects due to the reduced tumor burden and potentially less immunosuppressive tumor microenvironment.

Immunotherapy has shown significant promise in achieving long-term survival for not only hematologic cancers but also for solid tumors like melanoma and non-small cell lung cancer (NSCLC). The effectiveness and potential for long-term survival depend on various factors, including the type and stage of cancer, the specific immunotherapy used, and individual patient characteristics. Furthermore, biomarkers like programmed death-ligand 1 (PD-L1) expression can predict response to specific immunotherapies. Combining immunotherapy with other treatments, such as (neo) chemotherapy or radiation, can enhance effectiveness.

In this context, the phase 1 AMPLIFY-201 trial "Lymph-node-targeted, *mKRAS*-specific amphiphile vaccine in pancreatic and colorectal cancer" (4) is an example of an innovative vaccine for these cancers and lays the groundwork for extending this knowledge to other solid tumors by going beyond immune cell stimulation to include

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innovative strategies such as the targeted delivery to lymph nodes.

With AMPLIFY-201, Pant *et al.* (4) investigated a vaccine with targeted delivery to the lymph nodes for pancreatic and colorectal cancer (CRC) patients: the vaccine, ELI-002 2P, combined mutant Kristan rat sarcoma virus (mKRAS)-specific amphiphile peptides with a cytosin-phosphatidyc-guanin (CpG) oligonucleotide adjuvant. The primary endpoints of the phase 1 multi-cohort AMPLIFY-201 trial were the safety of the administered ELI-002 2P vaccine, the identification of the maximum tolerated dose (MTD), and the recommended phase II dose. These steps are crucial for establishing a solid foundation for the continued development of the vaccine in subsequent clinical trial phases. The secondary endpoints were the assessment of antitumor activity by evaluating circulating tumor DNA (ctDNA) and serum tumor antigens and relapse-free survival (RFS). By assessing these biomarkers, it is possible to gather early clues about the vaccine's biological activity and antitumor effects. Determining the RFS indicates the vaccine's potential effectiveness in preventing cancer recurrence, which is crucial for its potential clinical use. Both endpoints provide a comprehensive picture of the vaccine's therapeutic value and help to guide future clinical development.

Finally, *ex vivo* in the peripheral blood of patients throughout the study, the immunogenicity of ELI-002 2P was assessed directly as an exploratory endpoint. This assessment provides insights into how the vaccine activates the immune system. Specific immune pathways and responses triggered by ELI-002 2P could be identified by examining how immune cells respond to the vaccine.

ELI-002 2P demonstrated safety, induced robust T-cell responses, and reduced tumor biomarkers in 84% of all patients. The significantly prolonged RFS in recalcitrant Kirsten rat sarcoma viral oncogene homolog (KRAS)-mutated tumors correlated with increased T responses after vaccination.

The urgent need to develop treatments targeting the KRAS has been recognized for over four decades (5-7). KRAS is the most frequently mutated oncogene in a variety of highly lethal cancers, including pancreatic ductal adenocarcinoma (PDAC), CRC, and NSCLC (8). The presence of KRAS mutations in cancer patients has been associated with a poor response to standard therapies. Historically, due to its biochemical properties and the significant challenges encountered in drug-targeting efforts, KRAS was considered "undruggable". However, recent advancements have brought renewed hope with the emergence of covalently irreversible inhibitors, specifically against KRAS (G12C) mutation. In 2021, the first-in-class AMG510 (sotorasib) reached clinical trials showcasing optimistic results in patients with lung cancers with KRAS p.G12C mutation (9).

Recently, the Food and Drug Administration (FDA) granted conditional marketing authorization for Krazati (adagrasib) in combination with cetixumab as a targeted treatment option for adult patients with KRAS G12C-mutated advanced NSCLC. As a monotherapy, it was approved by the European Medicines Agency (EMA) later on for treating adult patients with advanced NSCLC with KRAS G12C mutation and disease progression after at least one prior systemic therapy (10,11). Moreover, a recent study has shown that combining sotorasib with panitumumab, an epidermal growth factor receptor (EGFR) inhibitor, can significantly improve progression-free survival in patients with chemorefractory KRAS G12C-mutated metastatic CRC (12). Despite these developments, the intrinsic resistance of KRAS frequently emerges as a significant obstacle, still limiting the overall clinical outcomes. The need to explore different approaches for targeting this critical oncogene remains an open question. Therefore, the strategy of priming the immune system to eliminate cells positive for specific KRAS mutations by administering long peptides is worth investigating.

One of the most relevant challenges of tumor-related peptides or proteins is the limited efficiency in delivery to the action side due to early degradation and lack of *in-situ* inflammatory response. In the AMPLIFY-201 trial, the G12D and G12R mKRAS peptides and the CpG oligonucleotide adjuvant were coupled to lipid chains. The resulting amphiphilic nature of the drug facilitates its interaction with albumin: the hydrophobic end binds to the hydrophobic pockets within the albumin molecule. In contrast, the hydrophilic end interacts with the aqueous environment. This forms a drug-albumin conjugate that can be more effectively delivered to the lymph nodes, where the peptides are released and bind to the antigen-presenting cells (APCs). This simple but effective targeted delivery method had previously only been demonstrated in mouse models; the current first-in-human study has opened the door to more widespread and enhanced targeted delivery. Furthermore, the entry of lipid chains into the lymph node could prolong their action, theoretically making this vaccine more effective. Although the safety profile has been well characterized

in the publication by Pant *et al.* (4), a more thorough examination of the albumin binding and lymph node inflammation is necessary for broader trials.

In the AMPLIFY-201 study, Pant *et al.* (4) were able to demonstrate a clinical application of the increasingly popular *in vitro* diagnostic device (IVD) for disease recurrence management: the early detection of MRD based on ctDNA and carbohydrate antigen 19-9 (CA 19-9) in blood plasma during follow-up after prior surgery. In contrast to the current standard of care, earlier treatment appears feasible after ctDNA-positive surveillance rather than waiting for radiological evidence of recurrence. This approach allows for more accurate disease monitoring and higher chances of increasing overall survival post-surgery, as follow-up therapy would become available at an earlier stage. Beyond the use of ctDNA as an early detection tool, which is undoubtedly a step forward in cancer monitoring, it is essential to confirm a substantial beneficial effect of ELI-002 and other upcoming vaccine therapies in an adjuvant setting after surgery in patients with MDR over patients with more advanced stages of the disease.

In line with the importance of early diagnosis for effective disease management, it is equally relevant to ensure that immunotherapy can induce a broad and specialized immunological profile to avoid tolerance and autoimmunity after subsequent administrations. The different types of emerging vaccination strategies, such as dendritic cell (DC) and messenger RNA (mRNA) vaccines or synthetic long peptide (SLP) vaccines, aim to overcome this challenge. The golden treatment remains elusive and is unlikely to have a straightforward outcome, as each approach exhibits different strengths.

mRNA vaccines have shown extraordinary performance against diseases like coronavirus disease 2019 (COVID-19) and have been extensively studied in cancer treatment in recent years (13). They are well-tolerated, easily degraded, and do not integrate into the host genome. As one would wish, these vaccines can induce both humoral and cell-mediated immunity, and technological advances are consistently improving mRNA-based vaccine stability, structure, and delivery methods. From a cost-effective perspective, the production of mRNA vaccines is fast and inexpensive compared to other approaches. While therapeutic mRNA-based cancer vaccines have not yet been approved for standard treatment, early clinical trials have shown solid results, such as Rojas *et al.*'s phase I trial of adjuvant autogenous cevumeran, an individualized neoantigen vaccine based on uridine mRNA-lipoplex nanoparticles (14).

Following a similar trend in recent years, DC-based vaccination has also seen significant development for cancer treatment (15). DCs are known as the most effective APCs and are responsible for primarily sensitizing naive T cells to specific antigens; these vaccines are typically generated using patient-derived DCs exposed to tumor-associated or -specific antigens (TAAs or TSAs) in the presence of immunostimulatory molecules to induce DC maturation, followed by reinfusion into patients. DC therapy has a safer profile than other cellular therapies, as it does not require lymphodepletion chemotherapy and does not pose a risk of CRS. Despite the effectiveness and safety of DC vaccines, the clinical response rate is relatively poor, calling for further vaccine optimization. Indeed, extensive efforts are being made to improve the immunogenicity and efficacy of DC vaccines. Similarly, SLP vaccines utilize TAAs derived from nonsynonymous mutations of tumor cells to target cancerous cells specifically (16). Major histocompatibility complex (MHC) class I molecules typically bind to peptides that are 8–10 residues in length, slightly longer for MHC II. Yet, it has been suggested that extending short peptides into long peptides can overcome immune tolerance and induce both $CD4^+$ and $CD8^+$ T cell responses, reaching immune profiles comparable to those in DC-based therapies. Given the response rate to the G12D and G12R mKRAS peptides was less than complete, it is still worth exploring whether incorporating neoantigens could lead to a more stimulating response, particularly as KRAS mutations are present in 25% of patients with solid tumors. Although offering mKRAS-positive patients an off-the-shelf treatment is attractive due to the potential for standardized and early production, it is essential to recognize the highly complex mutational profile that characterizes PDAC, among other cancers. Therefore, combining mKRAS peptides with TSAs previously identified from the patient's cancer tissue appears highly valuable. Since next generation sequencing (NGS) is already in the ELI-201 production pipeline, it could be further utilized for neoantigen identification. This can be combined with the latest in silico technologies to predict immunogenic profiles, including potentially stimulatory, specific epitopes from class I and II MHC molecules. This is one of the many aspects of the field that is advancing rapidly: several neoantigen identification pipelines are under development and further validation, including the application of artificial intelligence for the most accurate personalized reports (17). It remains clear that early treatment is critical to controlling disease progression.

Therefore, the preferred dosing regimen would be to start treatment shortly after the first signs of post-surgery relapse with the standardized mKRAS pool of SLP, followed by a combined vaccine with the neoantigens.

Other aspects may be considered for more mature versions of ELI-002 during its development. Foremost among these is expanding the range of mKRAS peptides included and investigating the optimal dose of the peptide in addition to the CpG-7909 DNA adjuvant. Pant *et al.* have adequately addressed these questions, which are likely to be answered in the already recruiting phase 2 AMPLIFY-7P trial (NCT05726864), which dosed its first PDAC patient last January. The trial aims to determine whether ELI-002 7P extends disease-free survival compared to observation, the current standard of care. Secondary objectives include evaluating the reduction and clearance of tumor biomarkers compared to baseline, assessing safety, median overall survival, and objective response rate per iRECIST in the crossover cohort, and evaluating the immunogenicity, number, and function of T cells induced by ELI-002 7P compared to baseline.

The combination with other immunostimulant adjuvants and drug delivery strategies, shown synergistic in several preclinical and early clinical studies, was not pursued further in the upcoming phase II trial. For instance, several clinical trials evaluated CEA/LAMP-1 (lysosome-associated membrane proteins) mRNA-engineered DC vaccines in glioblastoma patients in combination with various immune-modulating agents (NCT02529072, NCT00626483, NCT00639639). Similarly, following the trend of comparable mRNA and DC vaccines, combining SLP immunotherapy with immune checkpoint inhibitors (ICIs) such as anti-programmed death-1 (anti-PD-1)/PD-L1 may be a strategy worth considering for more optimal results (18). ICIs function by blocking checkpoint proteins from binding with their partner proteins, thus preventing the transmission of the 'off' signal. This allows T cells to target cancer cells effectively. Notably, a phase I study has reported on a mutant KRAS-targeted long peptide vaccine combined with ipilimumab/nivolumab in resected pancreatic cancer and mismatch repair deficiency (MMR)-proficient metastatic CRC (NCT04117087) (19).

Multiple factors can influence the efficacy and cycle of immunotherapy. Known factors affecting efficacy are tumor type [high tumor mutational burden (TMB)], microenvironment (level of immune cell infiltration), genetics [PD-L1 expression, microsatellite instability (MSI), and MMR], and the patient's immune system (immunocompetence). Treatment cycles can vary based on the patient's response, tolerance to the therapy, and side effects. Overall, patients with tumors with high PD-L1 expression, MSI-high, high TMB, good general health, and robust immune systems are known to benefit the most from immunotherapy. Whether this also applies to the ELI-002 2P vaccine needs further investigation.

Tumor- and class-specific patterns of immune-related adverse events (irAEs) occur when immunotherapies activate the immune system in a way that attacks normal tissues and cancer cells. By far, the most common irAEs in patients treated with vaccines is CRS, characterized by fever, fatigue, hypotension, and sometimes neurotoxicity. It is managed with symptomatic treatments and corticosteroids if needed. Immunotherapy with an immunogenic vaccine can sometimes have long-term effects on normal tissues due to the immune system's broad activity. Potential long-term impacts on normal tissue are generally caused by autoimmune reactions (e.g., hepatitis, colitis) or chronic inflammation (e.g., inflammatory bowel disease, chronic dermatitis). These adverse reactions could be monitored during follow-up by physical examinations, patient-reported outcomes, laboratory tests, imaging studies, and monitoring for symptoms of autoimmune or inflammatory conditions. Early detection of adverse reactions allows for timely intervention, mitigating long-term effects and improving patient outcomes.

Compared with younger patients, elderly patients face increased risks due to altered immune function, frailty, cognitive and functional decline, and severe comorbidities. Using multiple medications to manage these comorbidities can increase the risk of drug interactions and complicate the management of irAEs.

Overall, the work presented in AMPLIFY-201 contributes to the promising turnaround being experienced in cancer management and offers a solid foundation for the subsequent development of immunotherapies appropriately targeted to reach the lymphatic nodes. Although several open fronts remain unresolved and there is room for improvement, the path toward rapid, effective, non-invasive, and scalable treatments looks increasingly promising. We anticipate the outcomes of AMPLIFY-7P and the optimization of this treatment.

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